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# Comorbidity in Rheumatoid Arthritis: Pathogenetic Aspects and Patient Management Tactics

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**Annotation:** Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by systemic inflammation and multiorgan involvement. Recent studies demonstrate a high prevalence of comorbid conditions in RA patients, significantly affecting disease progression, prognosis, and treatment strategies. This review highlights the major types of comorbidities associated with RA, their pathophysiological links with inflammation, clinical manifestations, and therapeutic approaches. Special attention is given to cardiovascular disease, osteoporosis, infectious complications, depression, metabolic syndrome, and cancer risks.

**Keywords:** rheumatoid arthritis, comorbidity, cardiovascular diseases, depression, osteoporosis, infections, immunosuppression.

Rheumatoid arthritis (RA) is a chronic autoimmune inflammation of the joints that leads to multiple organ damage. According to world statistics, the prevalence of RA in the population is 0.5-1%. Despite the progress made in the treatment of RA patients in recent years, thanks to the introduction of biologics and JAK inhibitors, the presence of comorbid conditions is a significant obstacle to achieving sustainable remission. The importance of comorbidity is due to its effect on the course of RA, the effectiveness and safety of antirheumatic therapy, in addition, comorbid conditions can cause death in RA patients. In people suffering from rheumatoid arthritis, the mortality rate is 1.5-2 times higher than in the general population characterized by [1]. Recent studies have shown that the leading cause of decreased life expectancy in RA is cardiovascular complications associated with atherosclerotic vascular damage and thrombosis [2, 3]. Socially significant comorbid conditions in RA also include diseases of the gastrointestinal tract [4], osteoporosis, depression, and metabolic disorders [5, 6].

Taking into account the above, international recommendations, including the EULAR and the American College of Rheumatology (ACR), emphasize the need to assess and control comorbid conditions when choosing management tactics for RA patients [7].

## Research methods

This work is a review of the literature on the topic of comorbidity in RA. During the preparation of the article, an analysis of publications in the PubMed, Scopus and eLibrary databases for the period 2010-2024 was carried out. The keywords used were "rheumatoid arthritis", "comorbidity", "cardiovascular risk", "osteoporosis", "depression", "infection", "cancer", "inflammation", "biologic therapy". Articles in Russian and English were included.

## Discussion

RA has been found to be associated with an increased risk of myocardial infarction, stroke, and chronic heart failure. The risk of developing cardiovascular pathology in RA patients is due to the early development of atherosclerosis. These complications are based on processes associated with impaired endothelial function, the production of atherogenic cytokines (interlekin-6 (IL-6), tumor necrosis factor – α (TNF-α)), and hypercoagulation. Against the background of increased IL-6 and TNF-α, profound changes occur in the expression and function of potassium and calcium channels with prolongation of the QT interval, which is an independent risk factor for cardiovascular diseases [8]. Currently, new data has emerged on the role and significance of anticitrullinic antibodies in heart

disease. Citrullination of myosin and tropomyosin has been proven to alter their assembly and contractility patterns [9]. According to publications, patients with RA have dyslipidemia and increased atherogenicity [10]. A key role in the development of atherosclerosis is assigned to IL-1, which has procoagulant activity, causing the adhesion of monocytes and leukocytes to the vascular endothelium, the growth of vascular smooth muscle cells [11] and is able to induce the synthesis of IL-6. In addition, the use of certain anti-inflammatory drugs (for example, NSAIDs and GCS) also contributes to an increase in cardiovascular risk. Currently, biological therapy (especially TNF-α inhibitors) demonstrates a positive effect on the cardiometabolic profile.

One of the comorbid conditions in RA is the development of osteoporosis. Bone loss in patients with RA is caused by inflammation, decreased motor activity, and the use of glucocorticosteroids (GCS). Pro-inflammatory cytokines (IL-1, IL-6, TNF-α) lead to an imbalance in the system of transmembrane receptors and their RANKL/RANK/OPG ligands, which ensure the processes of intercellular interaction.IL-6 is a powerful inducer of RANKL (receptor activation of NF-kB ligand), which stimulates the maturation and differentiation of osteoclasts, causing bone resorption [12]. In addition, RA patients have a decrease in the blood concentration of osteoprotegerin (OPG), which blocks osteoclastogenesis. A violation of the RANKL/OPG ratio causes the development of osteoporosis in RA patients. The risk of osteoporotic fractures increases significantly when taking GCS, which reduce bone mineral density. In a meta-analysis, T.P. Van Staa et al. It was determined that the cumulative dose of systemic corticosteroids of 13.9 mg leads to a more pronounced than age-related loss. Minimization of GCS doses, regular densitometry, correction of vitamin D deficiency and the appointment of antiresorptive therapy are recommended for RA patients.

Depressive states often accompany rheumatoid arthritis, reaching 40%. According to modern concepts, the central mechanism of depression is a decrease in the concentration of norepinephrine, dopamine and serotonin in the synaptic cleft. In RA, direct exposure to a number of proinflammatory CCS leads to a decrease in the production of the amino acid tryptophan, which is a precursor to serotonin [13]. IL-6 contributes to the development of depression in RA patients, causing dysregulation of the hypothalamic-pituitary-adrenal system.

This condition worsens treatment adherence, increases the subjective perception of pain and reduces the quality of life. It is recommended to use the PHQ-9 and HADS scales, including psychotherapy and, if necessary, pharmacological correction.

Today, there is evidence of a pathogenetic relationship between metabolic syndrome and rheumatoid arthritis. The research results have confirmed that rheumatoid arthritis and metabolic disorders are inducers of the same physiological, morphological and immunological changes at different levels.

Inflammatory cytokines, in particular IL-6, regulate the interaction of insulin-sensitive tissues, intestinal L-cells and cells of the islets of Langerhans of the pancreas, contributing to the development of insulin resistance. Statistical analysis of the data showed that in patients with rheumatoid arthritis, insulin resistance is associated with higher concentrations of the N-terminal region of the brain natriuretic peptide (NT-pro-BNP) [14]. Additional risk factors for the development of metabolic syndrome and diabetes mellitus in RA patients are associated with the use of glucocorticosteroids. In a retrospective analysis of the data from the MOBILITY and TARGET studies, it was demonstrated that inhibition of IL-6 statistically significantly reduced the concentration of HbA1c as in diabetic patients[15].

## Conclusion

Comorbidity in RA is an essential component of the patient's management strategy, affecting the prognosis, treatment tactics, and complication rate. Effective management of RA requires an interdisciplinary approach that allows timely detection and control of concomitant diseases. The inclusion of comorbidity assessment in daily clinical practice contributes to the individualization of therapy and improvement of disease outcomes.

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